7. EPIDEMIOLOGIC STUDIES OF CARCINOGENICITY

This updated review presents the evaluation of studies published from 1985 through January 1997. The follow-up proposed by Lemen et al. (1990) of the cohort studied by Meinhardt et al. (1982) and Downs et al. (1992), an abstract submitted for the International Symposium are not reviewed in this evaluation. Lemen et al. (1990) did not present any results, while no details of study design and analysis were available for Downs et al. (1992). Since 1985, investigators have conducted studies of workers who produce 1,3-butadiene as a raw material (monomer production) or who use 1,3-butadiene in styrene-butadiene rubber (SBR) production (polymer production).

7.1. MONOMER PRODUCTION

7.1.1. Texaco Cohort

7.1.1.1. Downs et al., 1987: Mortality Among Workers at a Butadiene Facility

Investigators examined a cohort of 2,586 permanent male employees who worked a minimum of 6 months in a Texaco butadiene manufacturing plant (monomer production) that supplied the raw material to two adjacent SBR plants studied by Meinhardt et al. (1982) and for which an update has been proposed by Lemen et al. (1990). Data were available for the 37-year period from January 1, 1943, through December 31, 1979. Vital status of the cohort was determined through the Social Security Administration (SSA). Individuals whose vital status was unverifiable through SSA were traced through the Texas Department of Public Safety. Death certificates were obtained from the health departments of the states where the individual resided at the time of death. When this effort was unsuccessful, the individual's name was placed on a list, which was submitted to the health departments of Texas and Louisiana, to obtain the death certificates. A trained nosologist coded the death certificates using the eighth revision of the International Classification of Diseases (ICD).

Because quantitative exposure data had not been accumulated for individual workers, the investigators used department codes to construct a qualitative exposure scale composed of four groups: Group I, low exposure (included utility, office, and management workers, N = 432); Group II, routine exposure (included process, laboratory, storage, and transport workers, N = 710); Group III, nonroutine exposure (included skilled maintenance workers, N = 993); and Group IV, unknown exposures (N = 451). The investigators postulated that Group III workers may have had exposure to higher concentrations with a lesser frequency than Group II workers.

Of 2,586 employees in the cohort, 175 (6.8%) were black. Scrutiny of death certificates uncovered that 45 blacks (7.5% of total deaths) were improperly coded as whites. At this point, investigators conducted a preliminary analysis on the total cohort, using both black and white

national death rates. The standard mortality ratios (SMRs) were higher based on black rates as compared with white rates for four cause-specific deaths only (i.e., all lymphohematopoietic cancers) (SMR = 169 vs. 138), lymphosarcoma (SMR = 336 vs. 220), Hodgkin's disease (SMR = 135 vs. 102), and leukemia (SMR = 155 vs. 119). Most of the other SMRs for both cancers and noncancers were decreased based on black rates. Therefore, using black rates would have underestimated the risks. Thus, the entire cohort was treated as white, and all further analyses were conducted using white death rates.

Expected deaths were calculated using two referent populations: U.S. white males (national comparison) and white males in a seven-county area surrounding the plants (local comparison). The rates were standardized for age, race, sex, and calendar year. SMRs (labeled NSMR for national comparisons and LSMR for local comparisons) were calculated in the customary manner by dividing the observed deaths by the expected deaths and multiplying the ratio by 100. Under the null hypothesis, the significance of the ratios of observed to expected deaths was tested assuming that the observed (O) deaths followed a Poisson distribution using a two-sided test and assuming a p value of <0.05 to be significant. Comparisons between Groups I, II, and III were done by using the Mantel-Haenzel procedure for computation of relative risks in follow-up studies with stratified data (Rothman and Boice, 1982), and power calculations were performed using the normal approximation to the Poisson distribution (Beaumont and Breslow, 1981). The person-years at risk were not accrued until after the sixth month of employment.

A total of 64,800 person-years were accrued for the follow-up period. There were 603 deaths from 1943 through 1979; death certificates were obtained for 579 (96%) individuals. The vital status was unknown for 73 individuals (2.8% of the total cohort).

Results of this investigation indicated lower than expected mortality for these workers from all causes (NSMR = 80, $p<0.05$ and LSMR = 96, $p>0.05$, O = 603) and from all cancers (NSMR = 84, $p>0.05$ and LSMR = 76, $p<0.05$, O = 122). However, a site-specific comparison indicated a statistically significant increase in mortality from lymphosarcoma and reticulosarcoma (ICD code 200, NSMR = 235, 95% confidence intervals [CI] = 101-463, O = 8) compared with national rates and a nonsignificant excess (LSMR = 182, $p>0.05$) compared with local rates.

A comparison of wartime workers (N = 1,061; 452 deaths) who had worked for at least 6 months prior to 1945 and postwar workers (N = 1,525; 151 deaths) found an increase for all lymphohematopoietic cancers among wartime workers (NSMR = 150, 95% CI = 84-247, O = 15) and among postwar workers (NSMR = 134, $p>0.05$, O = 6). However, stratification reduced sample sizes considerably. The rationale for this comparison was based on the assumption that wartime exposures may have been higher than in postwar periods.

The analyses by duration of employment on mortality showed an increase among those who worked <5 years for all lymphohematopoietic cancers (NSMR = 167, p>0.05, O = 11), with most of the increase attributed to leukemia (NSMR = 187, p>0.05, O = 5) and residual lymphohematopoietic cancers[1] (i.e., non-Hodgkin's lymphoma, multiple myeloma, and other lymphohematopoietic cancers) (NSMR = 172, p>0.05, O = 5). Among those who worked >5 years, a nonsignificant increase was found for all lymphohematopoietic cancers (NSMR = 127, O = 10), mainly due to an increase in residual lymphohematopoietic cancers (NSMR = 200, O = 7).

Further analyses were conducted for the four groups identified on the qualitative exposure scale. For those with routine exposure (Group II), increases were noted for all lymphohematopoietic cancers (NSMR = 187, p>0.05, O = 6), Hodgkin's disease (NSMR = 197, p>0.05, O = 1), and residual lymphohematopoietic cancers (NSMR = 282, p>0.05, O = 4). An excess of kidney cancer (NSMR = 254, p>0.05) was also observed in this group based on one case. Similarly, in those with nonroutine exposure (Group III), excesses were observed for all lymphohematopoietic cancers (NSMR = 167, p>0.05, O = 10), Hodgkin's disease (NSMR = 130, p>0.05, O = 1), leukemia (NSMR = 201, p>0.05, O = 5), and residual lymphohematopoietic cancers (NSMR = 150, p>0.05, O = 4).

For those in the low-exposure group (Group I), excess mortality was seen for the same cancers (excluding Hodgkin's disease): all lymphohematopoietic cancers (NSMR = 128, p>0.05, O = 3), leukemia (NSMR = 105, p>0.05, O = 1), and residual lymphohematopoietic cancers (NSMR = 190, p>0.05, O = 2). In general, use of local southeast Texas coastal rates resulted in lower SMRs for the above three groups except for Hodgkin's disease in routine and nonroutine exposure groups, which showed slight increases over national rates. Both of these SMRs were based on one observed case in each group. None of the excess found in these three groups was statistically significant.

The comparison of Groups II, III, and IV with the low-exposure group (Group I) resulted in inconsistent findings due to a small number of cause-specific deaths and could not be reliably interpreted.

Analyses were also done by latency and number of years worked using national rates. Although the results for number of years worked were inconsistent for total cancers, the SMRs increased from 80 to 93, with increasing latency for this category. Similarly, excess SMRs for all lymphohematopoietic deaths were observed in all latency periods (0 to 9, 20 to 29, 30 to 39) except for 10 to 19 years. The number of years of employment results showed an inverse relationship for these cause-specific deaths. For cause-specific deaths due to lymphosarcoma and reticulosarcoma (ICD code 200), both the latency as well as number of years employed

[1]Residual lymphohematopoietic cancers include ICD codes 200, 202, 203, 208, and 209.

showed an inverse relationship. The notable finding in this analysis was for workers who had a latency of 0 to 9 years and had worked for less than 10 years (NSMR = 1,198, $p<0.01$, O = 4). This increase was statistically highly significant (tested by the author of this document using the Poisson distribution).

This is an extensively analyzed cohort mortality study. As correctly acknowledged by the investigators, there are a few methodological limitations to this study, the major ones being a lack of industrial hygiene (IH) data and a lack of personal work histories. In addition, half of the total cohort worked less than 5 years in the plant. Some of the workers from this cohort had also worked in two neighboring SBR plants. The exposures to other chemicals in the SBR plants and in their prior jobs are the confounders that were not adjusted for in this study. The cohort is relatively small to start with, but stratification in several subgroups further reduced the power.

The major strength of the study is that it is conducted in a butadiene (monomer) production facility in a cohort where confounding exposure from styrene is absent. The excesses observed are in cancers of the lymphohematopoietic system, which are consistent with cancer findings of the SBR plant workers. Most of the cases of malignancy are concentrated in workers employed for less than 10 years, which may be due to the occurrence of higher exposures during wartime years. The exposures during subsequent periods were lower. Thus, the finding of excess cancer mortality in short-term employees is not evidence against dose-response relationship.

7.1.1.2. Divine, 1990: An Update on Mortality Among Workers at a 1,3-Butadiene Facility*C*Preliminary Results

In 1990, Divine reported an updated analysis of the same Texaco plant (monomer production) cohort. The follow-up on the original cohort was extended through 1985 by updating the information on workers from company data and the SSA. Death certificates were obtained from the health departments of Texas, Louisiana, Ohio, and Mississippi and were coded by a trained nosologist according to the eighth revision of the ICD. The National Death Index records were searched for workers for whom the SSA failed to provide the vital status.

Mortality analyses were performed using Monson's computer program (Monson, 1974). Again, the white male death rates of the U.S. population were used due to uncertainties about race information in the company files and because there were few blacks in the cohort. Person-years were accrued similarly to the Downs et al. (1987) study.

The qualitative exposure categories remained the same. IH sampling data at the time of this study supported the exposure categories developed earlier. For this study, lymphosarcoma (ICD code 200) was reported separately from the cancers of other lymphatic tissues (ICD codes 202, 203, and 208).

A total of 74,219 person-years had accrued through 1985. The number of deaths had increased to 826, and death certificates were not available for 49 (6%) individuals. Of 2,582[2] employees in the cohort, 1,708 individuals were still alive and 48 (1.9%) were lost to follow-up. Overall, the pattern of results was unchanged from the report by Downs et al. (1987) for this cohort. For the total cohort, the SMRs for all lymphohematopoietic cancers and Hodgkin's disease were increased but not significantly; however, for lymphosarcoma and reticulosarcoma, the excess was significantly larger (SMR = 229, 95% CI = 104-435, O = 9) and accounted almost entirely for the increase in overall lymphohematopoietic cancers. Analyses by various subcohorts also yielded results similar to those observed in the earlier study (Downs et al., 1987). The highest increase was observed in lymphosarcoma and reticulosarcoma among workers who had worked more than 5 years but less than 10 years (SMR = 245, 95% CI = 79-572, O = 5). Prewar and postwar subcohort analyses demonstrated a statistically significant increase among the prewar subcohort for the same cause-specific deaths (SMR = 269, 95% CI = 108-555, O = 7), while an excess in the postwar subcohort was not statistically significant (SMR = 155, 95% CI = 17-558, O = 2).

Among the subcohorts based on exposure levels, the only statistically significant excess was observed for lymphosarcoma and reticulosarcoma among workers who were ever employed in routine exposure category (SMR = 561, 95% CI = 181-1,310, O = 5). Among workers who were ever employed in nonroutine exposure category, the excess was observed for all lymphohematopoietic cancers (SMR = 141, 95% CI = 70-253, O = 11) due to an increase in leukemia (SMR = 185, 95% CI = 68-403, O = 6). The lymphosarcoma in this group was slightly increased (SMR = 126, 95% CI = 14-454, O = 2).

For the total cohort, no pattern with latency or duration of years worked was observed for either all deaths or total cancer deaths. For all lymphohematopoietic cancers, excesses were observed in the latency groups of 30+ years (SMR = 205, O = 8) and 0 to 9 years (SMR = 200, O = 4). Both of these groups had worked less than 10 years. Deaths from lymphosarcoma were also increased in the same duration and latency groups. For 30+ year and 0 to 9 year groups, the SMRs were 3,333 (O = 2) and 1,333 (O = 4), respectively. No statistical test results were presented for this analysis. Similar analyses by different exposure groups failed to show any pattern for all lymphohematopoietic deaths and lymphosarcoma deaths among low-exposure and unknown exposure groups. Among routinely exposed groups, the excesses were observed for the same two latency and duration groups as for the total cohort, whereas for nonroutine exposure the excesses were observed only for 20 to 29 and 30+ years' latency groups who had

[2]It was not explained in the paper how the cohort was reduced to 2,582 from 2,586.

worked for less than 10 years. All of these excesses were based on ≤3 deaths in each group, making interpretation of these findings by exposure levels very difficult.

This also is a well-conducted study; unfortunately, the same methodological limitations that were present in the Downs et al. (1987) study are applicable to this study. However, the findings of this study are consistent with the earlier study, as well as with other SBR plant studies.

7.1.1.3. Divine et al., 1993: Cancer Mortality Among Workers at a Butadiene Production Facility

This update added another 5 years of follow-up to the earlier cohort of monomer workers (Divine, 1990). Cohort inclusion criteria remained the same but were extended from December 31, 1979, to December 31, 1990. This yielded additional workers resulting in a total cohort of 2,749 individuals. The four exposure groups were similar to those used in earlier studies with slight changes as follows: (1) The background exposure group (included office utility, warehouse, and transportation workers, N = 347). This group was called the low-exposure group in the previous two studies (Downs et al., 1987; Divine, 1990). (2) The low-exposure group (included workers from operating units, planners and engineers, welders, carpenters, and workers from brick masons, N = 958). This group was a combination of some of the low-exposure and all of the unknown exposure group from the previous two studies. (3) The nonroutine exposure group (included skilled maintenance workers such as pipefitters, tinsmiths, instrument and electrical workers, and insulators, N = 865). (4) The routine exposure group (included process, lab, storage, and transport workers, N = 1056). Although the last two categories appeared to be the same as in the earlier two studies, the change in the number of individuals in these categories was not explained in the paper. For this study, the investigators reviewed the results of the IH data and information obtained from the plant personnel and found that the main difference between the routine and nonroutine exposure groups was in the frequency and not the intensity of exposure.

Monson's computer program (Monson, 1974) was used for the analysis of this study also. All the analytical methods included use of white male death rates of the U.S. population (since there were very few blacks in the study, they were assumed to be white for the analysis) and calculation of person-years. The follow-up procedures and acquisition of death certificates were the same as in an earlier study by Divine (1990).

A total of 83,591 person-years was accrued. At the end of the follow-up period, 1,660 individuals were still alive, 38 were lost to follow-up, and 1,051 were deceased (death certificates were obtained for 1,036 individuals).

The overall results observed in this study were similar to the earlier two studies. The only statistically significant elevated SMR observed was for lymphosarcoma and reticulosarcoma for workers employed for less than 5 years (SMR = 286, 95% CI = 104-622, O = 6). Again, this increase probably came entirely from the prewar employees (SMR = 254, 95% CI = 102-523, O = 7). The analysis by exposure group showed an increase for the same cause in the routine exposure group (SMR = 452, 95% CI = 165-984, O = 6). The analysis by latency and duration of employment yielded the largest increase in 0 to 9 years latency for the individuals employed for less than 5 years (prewar individuals?). The SMR was 3,333 based on two observed cases. No statistical test results were presented for this analysis.

7.1.1.4. Divine and Hartman, 1996: Mortality Update of Butadiene Production Workers

This recent follow-up of the same cohort added 46 more individuals to the cohort (2,795) by extending the inclusion criteria and the follow-up period through December 31, 1994. The person-years accrued increased to 85,581. Of 2,795 individuals, 999 were still alive, 574 were lost to follow-up (28 known to be alive), and 1,222 were deceased (death certificates were obtained for 1,202 individuals). The follow-up procedures and analytical techniques (for SMR analysis) were the same as for earlier studies. The exposure categories also remained the same for this follow-up.

Based on IH data available since 1980, each employee's potential exposure to butadiene was estimated by separating the employee's work history by job categories into 1-year segments. Two variables were used to calculate the estimated exposure (job categories and calendar time periods). There were six exposure classes based on job categories: 0, 1, 2, 3, 4, and 5 with 0, 0.1, 0.2, 0.3, 0.4, and 0.5 weights (wt), respectively, and five calendar time periods: <1946 (wt = 10), 1946-59 (wt = 8), 1960-76 (wt = 4), 1977-85 (wt = 2), and 1986-94 (wt = 1). The cumulative exposure was obtained for each individual by summing up the scores for all the years of employment. These exposure estimates were used to conduct survival analyses for: (1) total lymphohematopoietic cancer, (2) lymphosarcoma, (3) non-Hodgkin's lymphoma, (4) multiple myeloma, and (5) leukemias.

Three different models were used for the survival analysis, i.e., a Cox proportional hazard model with a time-dependent estimate of cumulative exposure, a person-time logistic regression model with a time-dependent estimate of cumulative exposure, and a nested case-control model using conditional logistic regression. Each case had 10 matched controls by date of birth
($\pm$2 years). The selection of controls without replacement was from noncases at the time of the occurrence of each case.

The results of the SMR analyses were very similar to the earlier two follow-up studies of this cohort (Divine, 1990; Divine et al., 1993). The survival analyses failed to show any significant increase in the risk ratios, in any cause-specific cancer, by any of the three methods.

Although the investigators have done a good job of estimating the exposure and have conducted various analyses, the increase observed in the prewar subcohort for lympho-reticulosarcoma, when exposures were probably the highest, still persists. Upon completion of this study, this cohort has 52 years of follow-up but has failed to show any increase in leukemias which were observed in SBR production workers.

7.1.2. Shell Oil Refinery Cohort

7.1.2.1. Cowles et al., 1994: Mortality, Morbidity, and Hematological Results From a Cohort of Long-Term Workers Involved in 1,3-Butadiene Monomer Production

Shell Oil's Deer Park Refinery produced a butadiene monomer from 1941 to 1948 and 1970 to the present. The cohort consisted of male workers who had a minimum of 5 years employment in the jobs with potential exposure to butadiene or at least 50% of their total duration of employment (minimum of 3 months) in these jobs. This facility also had several other refinery operations and chemical production units. Three different analyses were performed on this cohort: (1) mortality, (2) morbidity, and (3) hematological.

1. Mortality Analysis:

A total of 614 employees comprised the cohort. The follow-up period was from 1948 to December 31, 1989. Vital status was assessed from company records, SSA, master beneficiary files, and the National Death Index (NDI). Death certificates were obtained for all the deceased workers and coded by a trained nosologist according to the revision of the ICD in effect at the time of death. Mortality rates of Harris County, TX, were used to compute the age-, race-, and calendar year-adjusted SMRs, using the Occupational Cohort Mortality Analysis Program (OCMAP) from the University of Pittsburgh.

A total of 7,232 person-years were accrued. Of 614 employees, 589 were still alive, 1 was lost to follow-up, and 24 were dead. No excess mortality, either for total deaths or total cancers (including cause-specific cancers), was observed.

2. Morbidity Analysis:

Original cohort members who were active at some time between January 1, 1982, and December 31, 1989, qualified for the morbidity study. Morbidity data were obtained from the Shell Health Surveillance System. The follow-up period was from 1982 to 1991. Causes of morbidity were coded according to the 9th revision clinical modification of the ICD. Morbidity

ratios (SMbRs) were calculated by using the internal comparison group of employees who were active during the same time period and had no exposure to butadiene.

A total of 438 employees were included in this analysis. No excess morbidity by any cause was observed.

3. Hematological Data Analysis:

Of 438 individuals included in the morbidity study, periodic hematological data were available for 429 individuals. These hematological data reveal that seven hematological outcomes were measured (between 1985 and 1991). The most recent laboratory test results were used for the analysis. Comparisons were done with similar results from 2,600 nonexposed employees. No differences were observed between butadiene-exposed vs. nonexposed groups.

This study has quite a few methodological limitations. The cohort is small, and deaths are few. The number of employees selected for this study from the time period 1941-1948, when exposure was probably higher, is unclear. Over 50% of the cohort was hired in 1970 or later, with an average follow-up of 12 years. This means that the cohort was still young, showing "healthy worker" effect, and enough latent period had not elapsed to show increases in cancers, which usually have a long latent period. Thus, despite the absence of any positive results, this study fails to provide any negative evidence towards the causal association between butadiene and occurrence of cancer.

7.1.3. Union Carbide Cohort

7.1.3.1. Ward et al., 1995: Mortality Study of Workers in 1,3-Butadiene Production Units Identified From a Chemical Workers Cohort

Ward et al., 1996c: Mortality Study of Workers Employed in 1,3-Butadiene Production Units Identified From a Large Chemical Workers Cohort

The study cohort was selected from 29,139 workers at three Union Carbide Corporation facilities in the Kanawha Valley, West Virginia. A total of 527 male workers who had worked between 1940 and 1979 were identified from the work history records as having ever worked in the departments where there was a potential for butadiene exposure. Only the individuals who worked in these departments during the butadiene production period (during World War II) were selected for the study (i.e., 364 individuals). The vital status was determined through December 31, 1990, using the National Death Index. Death certificates were obtained for decedents and coded according to the revision of the ICD codes in effect at the time of death. Both U.S. and Kanawha County mortality rates were used for comparison. A modified life table analysis developed by the National Institute for Occupational Safety and Health (NIOSH) was used to compute the SMRs.

Of 364 workers, 176 were alive, 3 were lost to follow-up, and 185 were dead at the end of 1990. The SMR for all causes was 91, while for all cancers it was 105. Neither of them were statistically significant. The only statistically significant increase was observed for lymphosarcoma and reticulosarcoma, which was based on four cases (SMR = 577, 95% CI = 157-148). A county-based comparison also resulted in a similar result. By duration of employment and latency, a statistically significant excess of the SMR was observed among workers who were employed for more than 2 years and with more than 30 years of latency (SMR = 1980, 95% CI = 408-5,780, O = 3).

The investigators stated that except for butadiene exposure, there were no common exposures to other chemicals in the four individuals who had died of lymphosarcoma and reticulosarcoma, although two of them had been assigned to an acetaldehyde unit for some time.

This study has a few methodological limitations. The cohort is very small, no adjustments for confounding exposures to other chemicals were done, and no exposure information is available. The qualitative exposure is assumed based on the job coded for butadiene exposure. It is still interesting to note that the exposure in these plants was to butadiene monomer alone either in the production process or the recovery from the olefin cracking process and not to styrene-butadiene polymer. The only other cohort exposed to butadiene monomer (Downs et al., 1987; Divine, 1990; Divine et al., 1993; Divine and Hartman, 1996) also found excess in lymphosarcoma and reticulosarcoma in the prewar subcohort.

Studies in monomer production workers are summarized in Table 7-1.

7.2. POLYMER PRODUCTION

7.2.1. Cohort Identified by Johns Hopkins University (JHU) Investigators

7.2.1.1. Matanoski and Schwartz, 1987: Mortality of Workers in Styrene-Butadiene Polymer Production

This cohort mortality study of SBR polymer production workers from eight plants (seven U.S. and one Canadian) was reviewed in a 1985 document (U.S. EPA, 1985). At that time, this study was submitted to the U.S. Environmental Protection Agency but was not published.

Table 7-1. Epidemiologic studies of the health effects of exposure to 1,3-butadiene Cmonomer production

Authors	Population studied	1,3-Butadiene exposure assessment	Results	Strengths and limitations
Downs et al. (1987)	2,586 permanent male employee cohort mortality Worked for at least a minimum of 6 months from January 1, 1943-December 31, 1979 Follow-up from 1943 through 1979 (37 years) Comparison group U.S. population (national) and 7 counties surrounding the plants (local)	Four exposure groups based on qualitative exposure scale: Group I, low (N = 432) Group II, routine (N = 710) Group III, nonroutine (N = 993) Group IV, unknown (N = 451)	SS NSMR = 235 and SNS LSMR = 182 for lymphosarcoma and reticulosarcoma for total cohort SS NSMR R = 1,198 for lymphosarcoma and reticulosarcoma for latency of 0-9 years and <10 years of employment	Cohort of monomer production workers, a major strength Lack of IH data ½ the cohort worked less than 5 years in the plant Relatively small cohort; therefore hard to interpret results after further stratification Lack of adjustment for confounding for people who worked in SBR plant too
Divine (1990)	Update of the cohort from Downs et al. (1987) Cohort reduced to 2,582 Follow-up extended through 1985 Comparison group U.S. population	Same exposure groups as the earlier study	For lymphosarcoma and reticulosarcoma: SS SMR = 229 for total cohort SS SMR = 269 for prewar subcohort SS SMR = 561 for routinely exposed for less than 10 years No pattern with latency or duration of employment	Same methodologic limitations as the earlier study

Table 7-1. Epidemiologic studies of the health effects of exposure to 1,3-butadiene Cmonomer production (continued)

Authors	Population studied	1,3-Butadiene exposure assessment	Results	Strengths and limitations
Divine et al. (1993)	Update of the cohort from Divine (1990) Cohort increased to 2,749 as the inclusion period extended through December 31, 1990 Follow-up extended through 1990 Comparison group U.S. population	Similar exposure groups as earlier with some redistribution of workers Group I, background (N = 347) Group II, low (N = 958) Group III, nonroutine (N = 865) Group IV, routine (N = 1,056)	For lymphosarcoma and reticulosarcoma SS SMR = 254 for prewar subcohort SS SMR = 286 for workers employed less than 5 years	Same strengths and limitations as earlier study
Divine and Hartman (1996)	Update of the cohort from Divine et al. (1993) Cohort increased to 2,795 as the inclusion period extended through December 31, 1994 Follow-up extended through 1994 Comparison group U.S. population Internal comparison	Based on IH data and work histories using • 6 exposure classes • 5 calendar periods Individual exposures were estimated for each worker Three different models used for the survival analysis	Results of SMR analysis were similar as earlier studies Survival analysis failed to show any SS excess in any cause-specific cancer	52 years follow-up Exposure estimation useful Major limitation is no exposure estimation available in prewar subcohort, which has the SS lymphosarcoma excess

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Table 7-1. Epidemiologic studies of the health effects of exposure to 1,3-butadiene Cmonomer production (continued)

Authors	Population studied	1,3-Butadiene exposure assessment	Results	Strengths and limitations
Cowles et al. (1994)	Cohort of monomer production workers from 1941-1948 and from 1970-1994 5 years or 50% of total duration worked in jobs with potential to 1,3-butadiene exposure Mortality follow-up from 1948-1989 (614 employees) Morbidity follow-up from 1982-1989 (438 employees) Hematologic data analyses 1985-1991 (429 employees)	None	No excess observed in either mortality or morbidity study No hematologic differences found between the exposed and nonexposed employees	Very small cohort Exposure is not certain Deaths are very few 50% of cohort hired after 1970 when exposures were low Not enough latent period has elapsed
Ward et al. (1995, 1996c)	Cohort of 364 male employees who had worked between 1940 and 1979 Employees who has worked in monomer production during World War II Follow-up through December 31, 1990 U.S. population Kanawha County population	Jobs where only 1,3-butadiene exposure occurred	For lymphosarcoma and reticulosarcoma SS SMR = 577 SS SMR = 1980 for more than 2 years of employment and 30 years of latency	Small cohort No adjustments for confounding exposures to other chemicals No exposure information available

SS = Statistically significant.
SNS = Statistically nonsignificant.
NSMR = National standard mortality ratios.
LSMR = Local standard mortality ratios.
IH = Industrial hygiene.

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Because the findings of the published study are essentially the same, it will not be reviewed again.

7.2.1.2. Matanoski et al., 1989: Epidemiologic Data Related to Health Effects of 1,3-Butadiene
Matanoski et al., 1990: Mortality of a Cohort of Workers in the Styrene-Butadiene Polymer Manufacturing Industry (1943-1982)

These two publications essentially reported the same updated reanalysis of the earlier cohort. In addition, Matanoski et al. (1989) also presented the results of the nested case-control study in this population. Three methodological differences in the original analysis (Matanoski et al., 1987) and the reanalysis presented in these two publications should be noted: extension of follow-up through 1982, fewer workers whose vital status was unknown (3.4% vs. 6.6% in the earlier report), and deletion of workers from the Canadian plant who had relatively short-term exposure (i.e., workers who had worked for less than 10 years or who had not reached the age of 45 during employment). Analytical methods were essentially unchanged from the earlier analysis.

In addition to information received from the SSA and the Motor Vehicle Administration, follow-up through local plant beneficiary records and the National Death Index was done to assess the vital status of the study cohort. Follow-up procedures for Canadian workers were similar to the earlier study. Death certificates were obtained from the local health departments. The total cohort was reduced from 13,920 to 13,422 in this study. Of 12,113 workers for whom the vital status was successfully traced, 23% (2,784) were still working in the plants, 53.4% (6,472) were alive but not working in the plants, 20.2% (2,441) had died, and vital status was unknown for 3.4% (416). The racial distribution was 75% whites, 10% blacks, 15% unknown (presumed to be white for the analysis), and less than 1% other.[3] Death certificates were obtained for 97.2% of the deceased individuals and were coded by a trained senior nosologist, using the eighth revision of the ICD.

Data analyses were done by using age, race, calendar time, and cause-specific U.S. population rates. A modified life-table program by Monson (1974) was used. The person-years were calculated through December 31, 1982. The first-year work experience was omitted from person-years because one of the inclusion criteria was that an individual had to have worked for at least 1 year. A total of 251,431 person-years were accrued, of which 226,475 were contributed by whites.

[3]The percentages, which are quoted from the paper, add up to 101. This is due to the rounding of the numbers by the authors of the paper.

Statistically significant lower SMRs for all causes of deaths (81) and for all cancers (85) were virtually the same as in earlier studies. The SMRs for all causes of deaths by 5-year calendar period demonstrated increasing SMRs with increasing time period, indicating a "healthy worker" effect in earlier calendar years. Blacks showed higher SMRs than whites in later years. A statistically significant excess for all causes of deaths was observed for blacks in the last 3 years of follow-up (SMR = 134, 95% CI = 101-175, O = 54). Most of the cause-specific cancer SMRs showed deficits in both races. A few cancer sites demonstrated excess mortality in both races. Among whites, excesses were observed for esophageal cancer, kidney cancer, Hodgkin's disease, and other lymphohematopoietic cancers. Among blacks, excesses were observed for stomach, liver, and prostate cancer; all lymphohematopoietic cancers; lymphosarcoma; leukemia; and other lymphohematopoietic cancers. None of the excesses were statistically significant.

Because the risks for kidney, digestive, and lymphohematopoietic system cancers approached those of the reference population, which was unusual for an occupational cohort with low overall risks, investigators further analyzed the data by work areas. For production workers, deaths from lymphohematopoietic cancers, Hodgkin's disease, and leukemia were nonsignificantly increased for the total cohort and among whites (except for leukemia). The only significant excess observed for the total cohort was for other lymphohematopoietic cancers, which included non-Hodgkin's lymphoma and multiple myeloma (SMR = 260, 95% CI = 119-494, O = 9). Among blacks, however, statistically significant excesses were observed for all lymphohematopoietic cancers (SMR = 507, 95% CI = 187-1,107, O = 6) and leukemia (SMR = 655, 95% CI = 135-1,906, O = 3). The other two excesses observed among blacks for lymphosarcoma and other lymphohematopoietic cancers (including non-Hodgkin's lymphoma and multiple myeloma) were based on one and two cases, respectively, none being statistically significant ($p>0.05$).

Among white maintenance workers, no excesses of lymphohematopoietic cancers were found with the exception of Hodgkin's disease (SMR = 170, 95% CI = 35-495), based on only three deaths. However, rates were nonsignificantly increased for digestive tract malignancies (i.e., esophagus, stomach, and large intestine). Among black maintenance workers, nonsignificant excesses were observed for cancer of the rectum and stomach. For utility workers, the numbers were reported to be too small to reach firm conclusions about risks. For the "other" category of workers (including laboratory workers, management, and administrative workers), excesses were observed for Hodgkin's (SMR = 130, 95% CI = 16-472, O = 2) and leukemia (SMR = 116, 95% CI = 43-252, O = 6) among whites and for leukemia (SMR = 246, 95% CI not given, O = 1) among blacks. Nonsignificant increased SMRs for the digestive

system among blacks were also observed for the stomach, liver, and pancreas, all of which were based on fewer than five cases.

Analysis by duration of work or latency for the total cohort did not show an increase in the hematopoietic cancers.

This is still the largest cohort of SBR workers. The increased follow-up, better tracing, and exclusion of short-term workers from the Canadian plant have resulted in demonstrating the excess mortality from malignancies of the lymphohematopoietic system, digestive system, and kidney. However, the limitations of the earlier study of this cohort (i.e., the lack of exposure data and inclusion of less than 50% of the population in the follow-up cohort) still exist. The magnitude of the bias introduced by exclusion of workers (2,391) due to missing information on total work history or crucial information such as date of birth could be substantial. Although an attempt was made to correct the race, the race was unknown for 15% of the eligible cohort, and this segment was assumed to be white for the analysis. This would result in an overestimation of rates in blacks and an underestimation of rates in whites. No explanation was given as to how the total eligible population of 13,422 was reduced to 12,113. No data were presented by individual plants, but as indicated in the earlier study, only four plants had follow-up starting from 1943, whereas in the other four plants the starting dates of the follow-up ranged from 1957 to 1970; thus, these latter four plants may not have had long enough follow-up for the malignancies to develop.

7.2.1.3. Matanoski et al., 1989: Epidemiologic Data Related to Health Effects of 1,3-Butadiene Santos-Burgoa et al., 1992: Lymphohematopoietic Cancer in Styrene-Butadiene Polymerization Workers

To elucidate the separate contributions of 1,3-butadiene and styrene to the cancers identified in the updated cohort study, a nested case-control study of this cohort of SBR workers was conducted using estimates of exposure to 1,3-butadiene and to styrene for each job. Fifty-nine cases and 193 controls (matched for duration of work) were included in the analysis. Among the case group were 26 cases of leukemia; 18 of other lymphatic cancers, which included 10 multiple myelomas and 7 non-Hodgkin's lymphomas; 8 Hodgkin's lymphomas; and 6 lymphosarcomas.

Cases (workers who had lymphohematopoietic cancer as either the underlying or contributory cause of death on death certificates) arose from the original eight plants with the same selection criteria for the eligibility of that cohort (13,422), with the exception of the Canadian plant. For the Canadian plant, the restriction of either 10 years of work or those who had reached age 45 during employment was dropped from the selection of cases, which added two more cases to lymphohematopoietic cancers. Another four cases were added in which

individuals had died of another cause of death but had a lymphohematopoietic cancer at the time of their death. Two cases were deleted from the final analysis, one lymphosarcoma due to lack of any controls and one non-Hodgkin's lymphoma due to lack of job records from which exposure could be identified.

Controls included workers from the same cohort who were alive or had died of any cause other than malignant neoplasms. Controls were individually matched to cases by plant; age; hire year; employment as long as or longer than the case; and, if the control was dead, then survival to the death of the case. Based on these criteria, an average of 3.3 controls per case were selected instead of 4 controls per case as intended by the investigators. This average of 3.3 controls per one case had more than a 90% chance of detecting the twofold risk from exposure to 1,3-butadiene. Both cases and controls had about 15 years of employment and were hired at 36 to 37 years of age, somewhat older than usually seen in occupational populations.

Exposures to 1,3-butadiene and styrene were calculated from the job records of each subject, the number of months that each job was held, and an estimate of the 1,3-butadiene and styrene exposure levels associated with that job. Both the job identification and exposure estimation were done independently and without knowledge of case or control status of the subjects. To estimate 1,3-butadiene and styrene exposures, all jobs within the rubber industry were ranked from 0 to 10 by a group of senior engineers with many years of experience in the industry. One-third of the jobs were determined to have no routine exposure, but almost all jobs were thought to have intermittent exposure. Cumulative dose for both styrene and 1,3-butadiene was calculated using the score and duration for each job in the participants' work history. Because the distribution of exposure scores was skewed to the right, a log transformation of the scores was used in the analyses. As the logarithmic transformation approached normal distribution, only the transformed exposure variables were used for the analyses.

Analyses were done by using "ever/never exposed" categories to both butadiene and styrene and using high-exposure vs. low-exposure groups (based on mean log exposure cumulative rank for each substance determined by combining cases and controls). Both conditional (matched) and unconditional (unmatched) logistic regression analyses were performed. Odds ratios (OR) for matched sets were then calculated based on maximum likelihood estimates of the OR, and test-based confidence limits around the OR were calculated.

Unadjusted for the presence of the other chemicals and unmatched, analyses by "ever/never exposed" to butadiene and styrene found significantly increased relative odds for leukemia for both high and low exposures. Relative odds for butadiene were 6.82 (95% CI = 1.10-42.23) and for styrene were 4.26 (95% CI = 1.02-17.78).

Nonsignificant excesses were also observed for all lymphohematopoietic, other lymphohematopoietic cancers for exposures to both butadiene and styrene. Other excesses were

for Hodgkin's disease among workers exposed to butadiene and lymphosarcoma among workers exposed to styrene.

Matched analyses demonstrated that risk for all lymphohematopoietic neoplasms was significantly increased among workers exposed to butadiene (OR = 2.30, 95% CI = 1.13-4.71). Separate evaluation of these neoplasms revealed that most of the association could be explained by a significant excess risk for leukemia (OR = 9.36, 95% CI = 2.05-22.94), but other cancers in this group were not significantly elevated. Leukemia also showed a threefold increase associated with styrene exposure (OR = 3.13, 95% CI = 84-112).

Conditional logistic regression was used to separate the risks associated with each of these substances. Again, there was a significant excess of leukemia associated with butadiene (OR = 7.61, 95% CI = 1.62-35.64) and a nonsignificant excess of leukemia associated with styrene exposures (OR = 2.92, 95% CI = 0.83-10.27). When exposures to both chemicals were evaluated in the model as dichotomous variables, only butadiene was found to be associated with leukemia (OR = 7.39, 95% CI = 1.32-41.33).

To determine if specific jobs within the SBR industry might explain some of the risk of leukemia, the investigators categorized each worker according to the longest job held. A mixed-job category that combined utilities, operation services, and laboratory jobs was associated with a relative odds of 3.78 (95% CI = 1.2-11.9). When butadiene was added to the model, the OR increased to 6.08 for the mixed-job category (95% CI = 1.56-23.72). The relative odds were 13.3 (95% CI = 2.24-78.55) for association between butadiene exposure and risk of leukemia adjusted for mixed jobs in this model. Thus, both the mixed-job category and exposure to butadiene seem to contribute to the risk of leukemia.

The trend test for increasing risk of leukemia with increasing exposure levels of butadiene (0 through 8) was statistically significant (trend = 3.76, p = 0.05). A similar trend was not found for styrene. The higher risk of leukemia seen in the original cohort for black workers could not be evaluated adequately because race was partially controlled in this nested case-control study.

Unlike the mortality study of this cohort, the case-control study did not show other lymphoma to be associated with production jobs, but the number of cases was small. Interestingly, when each chemical was analyzed by stratification, there was an excess risk for butadiene exposure when exposure to styrene was low (OR = 6.67, 95% CI = 1.06-42.7). A similar nonsignificant increase also was observed for styrene when butadiene exposure was low. This might have resulted from small numbers of non-Hodgkin's lymphoma or multiple myeloma included together with potentially different etiologies or correlated exposure data. Thus, investigators suggest further evaluation of each cancer in this other lymphoma category should be performed separately.

Investigators also caution that estimated exposures in this study were crude and were not substantiated by monitoring data. As correctly pointed out by them, the original ordinal rank does not create a perfect exposure scheme. The distribution of ranks was skewed to the right and had to be log-transformed to differentiate between no exposure and low exposure. Matching on duration of work may have overmatched the dose and resulted in underestimation of the risk. Validation of diagnosis of lymphohematopoietic malignancies was not done in this study, which is an important methodologic limitation of the study given the fact that lymphohematopoietic cancer recording on death certificates is unreliable (Percy et al., 1981). The panel ranked 71% of the jobs in ranks of two or less; thus misclassification of exposure based on the estimated exposure by job as judged by the panel members is quite possible. Because the panel members were blind concerning the status of the individual being the case or control, the distribution of misclassification should be the same in cases and controls.

7.2.1.4. Matanoski et al., 1993: Cancer Epidemiology Among Styrene-Butadiene Rubber Workers

This was an effort by the investigators to verify the findings of their earlier nested case-control study among styrene-butadiene production workers (Santos-Burgoa et al., 1992). This study had shown statistically significant elevated relative odds for leukemias. The results from the analysis conducted with a new set of three controls per case were similar to the results from the earlier study. The new controls were matched to all the variables except duration of work with the case. Comparability between the previous and new controls was checked by reviewing the information on cases and controls from the earlier study. To verify that the cause of death was correctly coded on the death certificates, hospital records for cases were obtained. Of the 55 records reviewed, two cases had been incorrectly coded on the death certificates as lymphohematopoietic cancers. Records were obtained for 25 out of 26 leukemia cases and were found to be correctly coded on the death certificates.

Exposure estimation was done based on measurements provided by seven rubber plants, the International Institute of Synthetic Rubber Producers, and NIOSH. Although there was variability among plants, a significant correlation was observed between the log transformed data provided by the company and the ranks of 464 job and area specific titles. Of the seven plants that provided exposure measurements for butadiene, three had geometric means. Thus, using the geometric means, the cohort data were reanalyzed for these three plants. The workers who were hired before 1960 and had 10 or more years of service showed excesses for all lymphohematopoietic cancers (SMR = 163, 95% CI = 113-227, O = 34) and leukemia and aleukemia (SMR = 181, 95% CI = 101-299, O = 15).

This reanalysis of earlier data with new information on exposure estimation validates the earlier results found by these investigators.

7.2.2. Cohort Identified by University of Alabama (UAB) Investigators

7.2.2.1. Delzell et al., 1996: A Follow-Up Study of Synthetic Rubber Workers

A retrospective cohort mortality study was conducted by Delzell et al. (1996) of synthetic rubber workers employed in seven U.S. and one Canadian plant. Of the eight plants, seven plants (including the Canadian plant) were studied by JHU (Matanoski and Schwartz, 1987; Matanoski et al., 1989, 1990, 1993; Santos-Burgoa et al., 1992) and one (two initial plants combined into one) by Meinhardt et al. (1982). Of seven plants studied by JHU, one located in Texas that had a starting time of 1970 was not included in UAB study. The cohort comprised all the male workers who had worked for at least 1 year between January 1, 1943, and January 1, 1992 (49 years), which was the end of the follow-up period. The follow-up period was shorter for plants 1, 2, and 6 because the complete records of the employees from these plants were available much later than 1943. The Canadian plant (plant 8) also had a shorter follow-up period because follow-up of men who had left employment before 1950 was not feasible.

Since the inclusion criteria for this study were different, there were some additions and deletions to the earlier study cohort. The vital status was assessed by using plant records; the SSA's death master file; the NDI; DMV records of Texas, Louisiana, and Kentucky for the U.S. plants; and plant records and record linkage with the Canadian Mortality Data Base for the Canadian plant.

Death certificates were acquired from plant and corporate offices and from state vital records. The underlying cause of death was coded by a trained nosologist using the ninth revision of the ICD. Any cancer was coded as a contributory cause of death. For the Canadian decedents, the underlying cause of death was used from Canadian death registration and coded according to the ICD revision in effect at the time of death. All ICD codes were converted to eighth revision codes for analysis. The Ontario Cancer Registry provided the information on incident cancer cases (including the date of diagnosis, primary site, ninth revision ICD code, and histologic classification) for the study period.

Mortality analysis included computation of SMRs using the U.S. male general and state population rates and Ontario male rates; SMRs by quantitative exposure (cumulative ppm-years and peak ppm-years) to 1,3-butadiene, styrene, and benzene; and stratified internal comparisons. Various within-cohort analyses were conducted using Poisson regression models.

This study included exposure estimation for each individual. A detailed description of this estimation appears in Section 7.2.2.2, Macaluso et al., 1996. Complete work histories were available for 97% of the cohort. Analysis for process group was conducted on the workers from

all the plants. Subgroup analyses were restricted to 6 plants (1,354 workers from 2 plants were excluded from the analyses due to the lack of information on specific work areas).

Of 15,649 males who had worked in SBR and related processes, 13,586 were white and 2,063 were black. Vital status assessment indicated that 10,939 (70%) workers were alive, 3,976 (25%) were dead, and 734 (5%) were lost to follow-up. Death certificates were acquired for 3,853 (97%) individuals. A total of 386,172 person-years (336,532 for whites and 49,640 for blacks) was accrued.

Total cohort analysis found SMRs of 87 and 93 for all causes and all cancers, respectively. The SMR for leukemia was 131 based on 48 observed deaths (95% CI = 97-174). The SMRs for lymphosarcoma and other lymphopoietic cancers were close to null.

Subcohorts of whites, blacks, ever hourly, and never hourly showed a similar pattern of below null results for both all causes and all cancer deaths. Ever hourly was the only subcohort in which statistically significant excesses were found for leukemia. The SMR was 143 (95% CI = 104-191, O = 36) for this subcohort. For white ever hourly workers, the SMR was 130 (95% CI = 91-181, O = 36), while for blacks the SMR was 227 (95% CI = 104-431, O = 9). The lymphosarcoma SMR for this subcohort was 102 based on 4 cases, while the SMR for other lymphopoietic cancer was 106 based on 17 cases. Neither of these excesses was statistically significant. The further analyses of this ever hourly subcohort by year of death (<1975, 1975-84, 1985+), year of hire (<1950, 1950-59, 1960), and age at death (<55 years, 55-64 years, 65+ years) showed statistically significant SMRs for 1985+ year of death (SMR = 187, 95% CI = 111-296, O = 18), 1950-59 year of hire (SMR = 200, 95% CI = 122-310, O = 20), and <55 years at death (SMR = 179, 95% CI = 104-287, O = 17).

When this subcohort was further restricted to >10 years of employment and >20 years since hire, the SMRs of 224 (95% CI = 149-323, O = 28) for all workers, 192 (95% CI = 119-294, O = 21) for whites, and 436 (95% CI = 176-901, O = 7) for blacks were observed. Furthermore, in this restricted subcohort, the SMRs for leukemia were 209 (95% CI = 100-385) and 228 (95% CI = 135-160) for the workers from plants with the solution polymerization process and workers from plants without such a process, respectively.

When analyses were done by various process groups, more than twofold increases were observed for leukemia in polymerization process SMR = 251 (95% CI = 140-414, O = 15), coagulation process SMR = 248 (95% CI = 100-511, O = 7), maintenance labor SMR = 265 (95% CI = 141-453, O = 13), and laboratory workers SMR = 431 (95% CI = 207-793, O = 10). Analysis by further restricting the process groups by 5+ years of employment and 20+ years since hire in each group showed the excesses in leukemia SMRs in the same processes as above.

Analyses by mutually exclusive process groups showed excesses for ever in polymerization and never in maintenance labor or laboratories (O/E = 8/4.7), ever in

maintenance labor and never in polymerization or laboratories (O/E = 6/3.7), and ever in laboratories and never in polymerization or maintenance labor (O/E = 8/1.6). Within the labor group, leukemia increase was observed for workers ever in maintenance labor and never in production labor (O/E = 11/3.8). On the other hand, for workers in production labor and never in maintenance labor, the leukemia excess was negligible (O/E = 2/1.4). No excess mortality from leukemia was observed among ever in finishing and never in polymerization process workers (O/E = 4/4.5).

An unpublished report by the same authors (Delzell et al., 1996) submitted to the International Institute of Synthetic Rubber Producers (IISRP) in October 1995 (Delzell et al., 1995) included many more results of the analyses of this cohort that are relevant to this assessment. A review of the unpublished results is presented in the following paragraphs.

Various analyses by estimated 1,3-butadiene and styrene exposures were conducted. The RRs calculated by Poisson regression for 1,3-butadiene ppm-years adjusted for styrene ppm-years, age, years since hire, calendar period, and race for 0, >0-19, 20-99, 100-199, and 200+ ppm-years were 1, 1.1, 1.8, 2.1, and 3.6, respectively. When analysis was restricted to leukemia as the underlying cause of death and person-years 20+ years since hire, the results were similar. Analysis restricted to ever hourly also showed positive results for butadiene. Various analyses were conducted by using alternate ppm-years categories of exposure. All the analyses consistently showed similar results, strengthening the association between 1,3-butadiene and occurrence of leukemias. It is interesting to note that all the leukemia subjects who were exposed to 1,3-butadiene were also exposed to styrene. There were only two leukemia cases who had exposure to styrene but none to 1,3-butadiene.

Analysis by 1,3-butadiene peak-years and styrene peak-years demonstrated an association with 1,3-butadiene peak-years and occurrence of leukemia when adjusted for styrene peak-years, 1,3-butadiene and styrene ppm-years, and other covariates. The association, however, was irregular. A similar analysis for styrene peak-years was weak and imprecise.

The investigators also conducted a cancer incidence study in the Canadian plant. Information was obtained from the Ontario Cancer Registry from 1965 to 1992. Standard incidence ratios (SIRs) were calculated by using the male general population of Ontario. No increased incidence was found for any cancer in this study.

This is a well-designed, -conducted, and -analyzed study. The main strengths of the study are large cohort size; long follow-up period (49 years); availability of exposure estimations on each individual, processes, and tasks; and in-depth analyses using both general population as well as internal comparison groups.

There are a few limitations as correctly pointed out by the investigators. The cause of death on death certificates was not confirmed by medical records. Histologic typing was not

available for leukemias. These limitations may have led to misclassification. Furthermore, as pointed out in the Macaluso et al. (1996) study, there may have been misclassification of exposure, but this was thought to be nondifferential. Two plants were eliminated from the final analysis due to the lack of detailed work histories. Although this may have resulted in fewer uncertainties, valuable data may have been lost due to this elimination. Nevertheless, the association between exposure to butadiene and occurrence of leukemia was present among both white and black workers and was fairly consistent across plants.

7.2.2.2. Macaluso et al., 1996: Leukemia and Cumulative Exposure to Butadiene, Styrene, and Benzene Among Workers in the Synthetic Rubber Industry

A cohort mortality study conducted in synthetic rubber workers by Delzell et al. (1996) (Section 7.2.2.1) had a component of exposure estimation. The exposures to 1,3-butadiene, styrene, and benzene were estimated by Macaluso et al. (1996).

An exposure estimation was conducted on each and every worker based on detailed work histories, work area/job specification, IH monitoring survey records, IH recommendations, various records from the plants, historical aerial pictures, use of protective and safety equipment, walk-through surveys, and interviews with plant management as well as long-term employees in specific areas/jobs. The quantitative exposure estimation was based on process analysis, job analysis, and exposure estimation. The job-exposure matrices (JEMs) were computed for 1,3-butadiene, styrene, and benzene, which were linked to work histories of each employee.

Quantitative estimates of exposure to 1,3-butadiene and styrene were based on background exposure plus task-specific exposure, using multiple exposure and point source models, respectively. Input variables for these models were derived from several information sources described earlier. Limited validation of exposure estimates was attempted by comparing the available IH data from the 1970s and 1980s as well as actually measuring the air concentrations of 1,3-butadiene and styrene under controlled conditions. The latter method showed a good agreement among the methods of sampling, while the comparison of IH data indicated overestimations of 1,3-butadiene exposure.

For each job, 8-h time-weighted average (TWA) intensities and the number of peak exposures (15-min exposures over 100 ppm) were calculated. Based on job exposures, a JEM database was developed that was linked with individual work histories to develop individual quantitative work exposure estimates. For each individual, the exposure indices were multiplied by the length of employment in that particular process or job and were added up for the total employment period in various jobs to estimate the cumulative exposure.

Mortality analysis was done by calculating the SMRs and risk ratios (RR) using estimated quantitative exposures to 1,3-butadiene, styrene, and benzene. Both cumulative ppm-

years and peak-years were calculated for each individual in the study. Person-year data were grouped by 1,3-butadiene, styrene, and benzene ppm-years for both SMR analyses as well as RR analyses. Comparability between cohort mortality rates and general population reference mortality rates was assured by limiting the SMR analysis to the individuals whose underlying cause of death was listed as leukemia (51 people). Risk ratios were computed by using the Mantel-Haenszel method and 95% CI were computed by the Breslow method. Poisson regression models were used for adjustment of multiple confounders and to compute within-cohort mortality rates, and the X^2 test for linear trend was used to examine the dose response.

Work histories were available for 97% of the population. Fifty-two in-depth interviews with plant management and long-term employees identified 446 specific tasks/work areas with potential for 1,3-butadiene, styrene, and benzene (3 plants only) exposure. Eight-hour TWAs for 1,3-butadiene, styrene, and benzene were 0-64 ppm, 0-7.7 ppm, and <1 ppm, respectively, the median exposures being <2 ppm for 1,3-butadiene and 0.5-1.1 ppm for styrene.

Exposure analysis found that 75% of the cohort was exposed to 1,3-butadiene, 83% was exposed to styrene, while only 25% was exposed to benzene. The median cumulative exposure to 1,3-butadiene, styrene, and benzene was 11.2, 7.4, and 2.9 ppm-years, respectively. The exposure prevalence as well as median cumulative exposure was higher in individuals who had died of leukemia. Among the leukemia decedents, 85% had exposure to 1,3-butadiene, with their median cumulative exposure being 36.4 ppm-years. This exposure was two times higher as compared with all decedents and three times higher as compared with all the other employees. The exposure to styrene was present in 90% of leukemia decedents, with median cumulative exposure in them being 22.4 ppm-years, two times and three times higher as compared with all the decedents and all other employees, respectively. Benzene exposure was found to be less frequent among leukemia decedents as compared with all the other employees. Analysis by benzene exposure showed no association with the occurrence of leukemia after adjustment for 1,3-butadiene and styrene.

Leukemia SMRs increased with increasing cumulative exposure to 1,3-butadiene as well as styrene. Mortality RRs computed for cumulative 1,3-butadiene exposure adjusted for race, age, and cumulative styrene exposure also showed increasing RRs for increasing cumulative exposure to 1,3-butadiene. The adjusted RRs for cumulative exposures of butadiene of 0, <1, 1-19, 20-79, and 80+ ppm-years were 1, 2.0, 2.1, 2.4, and 4.5, respectively. The linear X^2 test for trend was statistically significant ($p = 0.01$). When similar RRs were computed for styrene exposure, neither showed a consistent pattern nor a trend of increasing risk with increasing exposure. A similar trend test was statistically not significant.

Analysis by exclusion of the nonexposed population resulted in RRs of 1, 1.5, and 1.7 for 0.1-19, 20-79, and 80+ ppm-years of the cumulative exposures of 1,3-butadiene. The linear

trend test was statistically significant ($p = 0.03$), substantiating the earlier finding of increasing risk of leukemia with increasing cumulative exposure to 1,3-butadiene. Although the same analysis suggested increasing risk of leukemia with increasing cumulative exposure to styrene after adjustment for 1,3-butadiene and other covariates, the results were imprecise and statistically nonsignificant.

There was neither any positive or negative interaction found between the cumulative exposures to 1,3-butadiene and styrene.

For the last decade or so, epidemiologists have been including exposure estimation in their studies. The methods used and efforts made to do exposure estimations are improving but variable. This study is one of the best efforts of exposure estimations to date. The investigators have used many available methods to come up with best estimates of exposures of 1,3-butadiene, styrene, and benzene. They also have validated these estimates on a smaller scale. Although this is considered as the best effort, it should be noted that these are estimates and not actual measurements. Two plants were eliminated from the analysis because detailed work histories were lacking. Thus it is possible that individuals may have been misclassified with respect to process or job, resulting in either over- or underestimations of exposure. However, there is no reason to believe that the misclassification of exposure occurred only in individuals who had died of leukemia.

Studies in polymer production workers are summarized in Table 7-2.

7.3. SUMMARY AND DISCUSSION

1,3-Butadiene has been shown to be both mutagenic as well as carcinogenic in animals and humans. Data in animals, particularly in mice, show that butadiene is a multisite carcinogen

Table 7-2. Epidemiologic studies of the health effects of exposure to 1,3-butadiene Cpolymer production

Authors	Population studied	1,3-Butadiene exposure assessment	Results	Strengths and limitations
Matanoski et al. (1989 and 1990)	Update of the cohort from Matanoski and Schwartz (1987) Cohort mortality of 8 SBR polymer production plant workers Reduced cohort of 13,422 followed through 1982 Worked for at least 1 year Comparison group U.S. population	Divided in four major areas based on the longest job held: Production workers Utility workers Maintenance workers All other work sites	Among production workers: SS SMR = 260 for other lymphohematopoietic cancers in whites SS SMR = 507 for all lymphohematopoietic cancers and SS SMR = 655 for leukemia in blacks No relation observed with latency or duration of employment	Largest cohort mortality study of SBR workers Lack of exposure data Exclusion of 50% of the population in the follow-up Four plants had follow-up ranging from 12 years to 25 years; may not be enough time for malignancies to develop
Matanoski et al. (1989) Santos-Burgoa et al. (1992)	Nested case-control study Cases: - of leukemia 26 - of other lymphatic cancers 18 Controls matched on: plant, age, hire year, employment duration, survival to the death of the case an average 3.3 controls (instead of intended 4) were selected	Exposure to 1,3-butadiene and styrene was done by job identification and levels associated with that job Estimations of job and exposure levels were done independently of the status of the case or control The jobs were ranked from 0 to 10 Cumulative dose was calculated using the score and duration for each job	For 1,3-butadiene: $ Ever/never exposure SS OR = 6.82 (high) and 4.26 (low) were found for leukemia $ Matched analyses SS OR = 2.3 for all lymphohematopoietic cancer SS OR = 9.36 for leukemia $ Conditional analyses	One of the strengths is attempt was made to estimate actual exposure Matching may have overmatched the dose Lack of validation of diagnosis of hematopoietic malignancies may have resulted in misclassification Misclassification of exposure based on job categories

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Table 7-2. Epidemiologic studies of the health effects of exposure to 1,3-butadiene Cpolymer production (continued)

Authors	Population studied	1,3-Butadiene exposure assessment	Results	Strengths and limitations
Matanoski et al. (1989) Santos-Burgoa et al. (1992) (continued)		A log transformation of the scores was used in the analyses Analyses were done: - by ever/never exposed - by high- vs. low-exposure - both matched (conditional) and unmatched (unconditional)	SS OR = 7.61 for leukemia $ SS OR = 6.67 for other lymphoma when styrene exposure was low SS trend of 3.76 was found for increased risk of leukemia with increasing exposure levels of butadiene	
Matanoski et al. (1993)	Same as nested case-control study A new set of 3 controls per case Cause of death verified by hospital records Cohort data reanalysis	Exposure estimation done based on measurements provided by seven plants, IISRP, and NIOSH	Similar results with new controls Reanalysis of cohort data for three plants SS SMR = 163 for all LHC SS SMR = 181 for leukemia and aleukemia	Verification of cause of death New set of controls validates earlier results

Table 7-2. Epidemiologic studies of the health effects of exposure to 1,3-butadiene Cpolymer production (continued)

Authors	Population studied	1,3-Butadiene exposure assessment	Results	Strengths and limitations
Macaluso et al. (1996)	Cohort of seven U.S. and one Canadian SBR workers mortality study Worked for at least 1 year between January 1, 1943, and January 1, 1992 Follow-up period through January 1, 1992 15,649 male workers U.S. population Respective State populations where the plants were located Ontario male rates for Canadian plant Internal comparison using Poisson regression	Exposure estimation conducted based on several information sources including IH Quantitative exposure estimates on background, task-specific, multiple exposure, and point sources models for 1,3-butadiene, styrene, and benzene Peak exposures 8-h time-weighted intensities Cumulative exposures Exposures estimated for each individual	Adjusted RRs for cumulative exposure to 1,3-butadiene of 0, <1, 1-19, 20-79 and 80 + ppm-years were 1, 2.0, 2.1, 2.4, and 4.5. Trend test was SS Exclusion of the nonexposed population also had similar results with SS trend test	Methods used and efforts made for exposure estimation are best efforts to date Misclassification with respect to job may be possible but unlikely to be only in leukemia deaths

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Table 7-2. Epidemiologic studies of the health effects of exposure to 1,3-butadiene Cpolymer production (continued)

Authors	Population studied	1,3-Butadiene exposure assessment	Results	Strengths and limitations
Delzell et al. (1996)	Same as Macaluso et al. (1996)	Same as Macaluso et al. (1996) Analysis by ever-hourly and never-hourly Analysis by process groups	Ever-hourly workers showed for leukemia SS SMR = 143 for all ever-hourly workers SS SMR = 227 for blacks SS SMR = 187 for 1985+ year of death SS SMR = 200 for 1950-59, year of hire SS SMR = 179 for <55 years age at death SS SMR = 224 for >10 years of employment and >20 years since hire (SMR = 192 for whites and SMR = 436 for blacks both SS) Various process groups showed for leukemia SS SMR = 251 for polymerization process SS SMR = 265 for maintenance labor SS SSMR = 431 for laboratory worker Cancer incidence study in Canadian plant did not show any increased incidence for any cancer	Same as Macaluso et al. (1996) Cause of death not verified Histologic typing of leukemia not available, thus leading to misclassification

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Table 7-2. Epidemiologic studies of the health effects of exposure to 1,3-butadiene Cpolymer production (continued)

SS = Statistically significant.
SMR = Standard mortality ratio.
IH = Industrial hygiene.
RR = Risk ratios.
OR = Odds ratio.
LHC = Lymphohematopoietic cancers.

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even at the lowest dose of 6.25 ppm (NTP, 1993). Occupational populations are exposed to butadiene in the production/recovery of butadiene monomer and production of resins and plastics. Exposure to this colorless, odorless gas is entirely via inhalation due to its extremely volatile nature. The general population is exposed to butadiene in ambient air, the major sources of its release in ambient air being automotive exhaust and cigarette smoke. Its potential to cause cancer in humans has become an important public health issue.

Butadiene becomes diluted in ambient air and is eliminated by photooxidation. Thus it is difficult to study the health effects of exposure to butadiene in the general population. Since exposure to butadiene is ubiquitous in the general population, "unexposed" reference populations used in occupational cohort studies are likely to contain a substantial number of individuals who are exposed to butadiene nonoccupationally. Furthermore, the issue of health measurement is complicated by the fact that occupational cohorts tend to be healthier than the overall general population and have below average mortality, which is referred to as the "healthy worker effect." Thus the standard mortality ratios observed in occupational cohorts, computed using the general population as the reference group, are underestimations of real risk.

7.3.1. Monomer Production

To evaluate the carcinogenicity of 1,3-butadiene, cohorts from monomer and polymer production were studied by several investigators. The largest cohort of monomer production workers was initially studied by Downs et al. (1987) and had three follow-ups by Divine (1990), Divine et al. (1993), and Divine and Hartman (1996). The cohort included 2,586 workers initially and had 2,795 individuals in the last follow-up due to an extended time period for the inclusion criteria. The four exposure groups were identified by Downs et al. (1987) based on a qualitative exposure scale. They remained the same in Divine's (1990) follow-up and were similar but slightly changed in Divine et al. (1993). In their last follow-up, based on IH data, the investigators (Divine and Hartman, 1996) estimated the potential exposure to butadiene for each employee by their work histories (in 1-year segments), using job categories and calender time periods. Cumulative exposures were obtained by summing the scores of all the years of employment.

The findings of all four investigations were essentially the same even after 52 years of follow-up. There were deficits observed for mortality from all causes and all cancers. The only statistically significant excess observed was for lymphosarcoma (ICD code 200). Downs et al. (1987) observed this excess for the total cohort and for the subcohort of workers who had worked for less than 10 years and latency of 0-9 years. This excess was seen in the prewar subcohort in all three follow-up studies (SMR = 269, and SMR = 254 in both Divine, 1990, and in Divine et al., 1993; Divine and Hartman, 1996). No information on exposure levels was

available for this period, but it was believed that the exposures were high during the prewar period. When analyses were done by years of employment and latency excess for lymphosarcoma, mortality was always found to be in individuals employed for less than 10 years and with latency of 0-9 years. It should be noted that after 52 years of follow-up, no elevated mortality was observed for leukemia, which was the main finding in SBR workers.

A small cohort of 364 individuals was identified from 29,139 workers at three Union Carbide Corporation plants who had potential exposure to butadiene during World War II (Ward et al., 1995, 1996c). The exposure to butadiene was assumed based on job categories, and no adjustments for confounding by other chemicals were done. As observed in the Divine Studies (1990, 1993, 1996), a statistically significant excess for lymphosarcoma (SMR = 577) also was observed in this cohort.

A third cohort of 614 workers exposed to monomer was studied by Cowles et al. (1994) and the study failed to show any excess mortality or morbidity. Due to several methodologic limitations, this study failed to provide any negative evidence towards the causal association between exposure to butadiene and occurrence of lymphosarcoma that was observed in the other two cohorts.

7.3.2. Polymer Production

A further follow-up and reanalysis of a large SBR polymer production workers' cohort (Matanoski and Schwartz, 1987) was conducted by Matanoski et al. (1989, 1990). This follow-up added 3 years to the earlier study. The findings of this follow-up were essentially the same as the earlier study. The only statistically significant excesses were found among production workers. Among whites the excess was for other lymphohematopoietic cancers (SMR = 260) and among blacks the excesses were for all lymphohematopoietic cancers (SMR = 507) and leukemia (SMR = 655). Analyses by duration of work and latency did not show any increases in hematopoietic cancers. There were no exposure measurements or estimations done in this study.

A nested case-control study from this cohort (Matanoski et al., 1989, 1990) was conducted by the same investigators and reported in Matanoski et al. (1989) and Santos-Burgoa et al. (1992). Fifty-nine cases of lymphohematopoietic cancers and 193 matched controls were identified. Exposures to 1,3-butadiene and styrene were estimated in these individuals using the job records and levels of exposures to 1,3-butadiene and styrene associated with those jobs independently of the case or control status. The jobs were ranked and cumulative dose was calculated for each case and control. Analyses were conducted using log transformed scores. The relative odds were increased for high (OR = 6.82) and low (OR = 4.26) exposures in the ever/never exposed analysis, matched analysis (OR = 9.36), and conditional analysis (OR = 7.61) for leukemia. All the increases were statistically significant. A statistically significant

trend was also observed for increasing risk of leukemia with increasing exposure levels of butadiene.

Because the findings of the nested case-control study were questioned by Acquavella (1989) and Cole et al. (1993), as they were in disagreement with the base cohort study, Matanoski et al. (1993) reevaluated the analysis of the nested case-control study by choosing a new set of three controls per case. The investigators also verified the cause of death by obtaining the hospital records. The findings of the new analysis were similar to the earlier analysis.

Furthermore, they estimated the exposures to the cohort based on measurements provided by seven rubber plants, IISRP, and NIOSH. In an analysis of the subcohort from three plants who had the geometric means of exposure, statistically significant excesses were observed for all lymphohematopoietic cancers (SMR = 163) as well as for leukemia and aleukemia (SMR = 181).

Delzell et al. (1996) and Macaluso et al. (1996) reported separately the two components of the follow-up study of synthetic rubber workers. These investigators studied the seven plants studied by Matanoski and Schwartz (1987), Matanoski et al. (1989, 1990, 1993), and Santos-Burgoa et al. (1992) and one plant (two initial plants combined into one) by Meinhardt et al. (1982). The follow-up period was 49 years. Investigators estimated the exposures to 1,3-butadiene, styrene, and benzene for each worker. This was done by using various means such as job histories, work areas, IH data, historical plant data, aerial pictures, interviews with long-term employees and managers, walk-through surveys, etc. Quantitative exposures were calculated and limited validation of exposure estimates were attempted using available 1970's and 1980's IH data. Cumulative and peak exposures were calculated for each worker. Comparison with the U.S. population resulted in statistically significant excesses for leukemia in ever-hourly workers (SMR = 143) and its subcohort of blacks (SMR = 227). The excesses were also found in the ever-hourly cohort for year of death (SMR = 187 for 1985+), year of hire (SMR = 200 for 1950-59), age at death (SMR = 179 for <55 years), and for more than 10 years employment and more than 20 years since hire (SMR = 192 for whites and SMR = 436 for blacks). Laboratory workers, maintenance workers, and polymerization workers also showed increased SMRs of 431, 265, and 251, respectively. All these analyses were done adjusting for styrene and benzene. When internal comparison was done using the estimated ppm-years exposure data, relative ratios increased with increasing exposures. The trend test was statistically significant.

The incidence study conducted in the Canadian plant employees did not show any increases in any cause-specific cancers.

7.3.3. Relevant Methodologic Issues and Discussion

Throughout this chapter, various methodologic issues including strengths and limitations are discussed. The major concerns are lack of exposure information and short follow-up periods in earlier studies, small cohort size, lack of data on confounding variables, and lack of latency analysis in one study. Furthermore, death certificates were used by all the investigators, which could lead to misclassification bias. Validation of diagnosis of lymphohematopoeitic cancer was not done in any of the studies except in Matanoski et al. (1993). This is a methodologic concern given the fact that lymphohematopoeitic cancer recording on death certificates is unreliable (Percy et al., 1981).

Lack of exposure information is another major limitation in Cowles et al. (1994) and Ward et al. (1995, 1996c). Cowles et al. (1994) made no attempt to even do job classification. This cohort was very small, there were very few deaths, and more than 50% of the cohort had an average follow-up of 12 years.

Ward et al. (1995, 1996c) also did not attempt any exposure estimation. This cohort also was very small but was restricted to workers who had worked in the 1,3-butadiene production period (during World War II). The high SMR for lymphosarcoma and reticulosarcoma observed in this study was based on only four cases. They used employment of 2 years+ as surrogate for exposure and stated that there were no other common exposures to other chemicals. Considering that the cohort was small and only four deaths occurred from lymphosarcoma and reticulosarcoma, it should be noted that this finding is consistent with the finding of the other monomer facility studied by Divine (1990), Divine et al. (1993), and Divine and Hartman (1996).

A monomer cohort study conducted by Downs et al. (1987) and followed by Divine (1990) and Divine et al. (1993) also lacked exposure information, although the surrogate exposure grouping was done by qualitative exposure information based on job descriptions/work areas. The investigators attempted the exposure estimation in their last follow-up (Divine and Hartman, 1996) and found that except for an excess observed for lymphosarcoma and reticulosarcoma in the prewar subcohort, there were no excesses in any cause-specific cancer mortality. However, investigators did not have any information on work histories or levels of 1,3-butadiene exposure during the prewar period, which made exposure estimation in the prewar workers impossible. Even after 52 years of follow-up and extensive analyses, this cohort has not observed any excess in mortality from leukemia that was observed in SBR workers. Nonetheless, the finding of excess mortality from lymphosarcoma and reticulosarcoma is consistent with findings of Meinhardt et al. (1982) and Ward et al. (1995, 1996c). In addition, the excess of lymphosarcoma and reticulosarcoma in short-term workers but not in long-term workers was consistent with the similar findings of Meinhardt et al. (1982).

Matanoski and Schwartz (1987) and Matanoski et al. (1989, 1990) did not have any exposure information available. The cohort was distributed in four major areas based on longest jobs held and the qualitative exposure information used as surrogate. When the nested case-control study was undertaken by these investigators (Matanoski et al., 1989; Santos-Burgoa et al., 1992), exposure estimation was done by using various sources only for the selected cases and controls. They observed a statistically significant high excess from leukemia mortality, which the authors concluded as being causally associated with exposure to 1,3-butadiene.

Matanoski et al. (1993) validated their earlier results of the nested case-control study by using a new set of three controls per case. They also verified the cause of death noted on the death certificates and diagnosis noted on the hospital charts. They found that the diagnosis noted on 25 out of 26 charts agreed with the cause of death noted on the death certificates. The results of this study were similar to the earlier nested case-control study.

This finding of a high excess of leukemia mortality in the case-control study was questioned by Acquavella (1989) and Cole et al. (1993) because no excess leukemia mortality was found in the base cohort study from which the cases and controls were selected. Their argument that the results of the case-control study were statistically incompatible with the results of the cohort study was based on the calculations of number of leukemias that should have been seen in the cohort study, based on the relative odds observed in the case-control study. The Cole et al. (1993) calculations resulted in approximately 104 leukemia cases if relative odds of 7.6 were applicable to 60% of the cohort that was exposed to 1,3-butadiene and an additional 9.2 expected leukemias for the remaining 40% cohort that was not exposed, resulting in an observed 113 leukemias for the cohort as against 22 leukemias actually observed in the cohort study. Variability in both the prevalence of exposure and the relative odds were looked at by these authors (Cole et al., 1993), and they concluded that there was no reasonable combination that resolved the incompatibility between the findings of the cohort and case-control studies.

Matanoski and Santos-Burgoa (1994) disagreed with this criticism. They asserted that the 60% exposure observed among the controls in the case-control study overestimated the prevalence of exposure for the cohort population and that the matching criteria may have skewed the control selection and produced controls who were not representative of the base cohort.

The main limitations of the cohort study were that more than 50% of the population was excluded due to lack of work histories or start date and lack of exposure data. The follow-up for four plants where the starting date was 1957 to 1970 may not have been long enough for malignancies to develop. As far as the nested case-control study is concerned, as pointed out by the authors, the estimated exposures were crude and were not substantiated by IH data. The exposure misclassification may have occurred based on the estimated exposure by job if the jobs were incorrectly identified for higher or lower exposure. However, the panel members were

blind towards the status of cases and controls, thus the distribution of misclassification should be the same in cases and controls.

Although the controversy about the cohort and case-control study is still not resolved, the nested case-control study was the first one to demonstrate a strong association between exposure to 1,3-butadiene and occurrence of leukemias.

The Delzell et al. (1996) and Macaluso et al. (1996) cohort study is one of the best efforts of exposure estimation to date. Some misclassification of exposure may have occurred with respect to certain jobs, but it is unlikely to have occurred only in leukemia cases. The investigators also did some validation of exposure estimates based on IH data. They pointed out correctly that the excess mortality observed for leukemia was based on death certificates and was not verified by medical records. Histologic typing of leukemia was also not available. This may have resulted in misclassification. Two plants were eliminated from the final analysis due to the lack of work histories, which may have resulted in the loss of valuable data.

Based on these monomer and polymer production worker cohorts, it is obvious that an increased number of lymphohematopoietic cancers is observed in these populations. A clear difference is becoming apparent though. Increased lymphosarcomas develop in workers exposed to monomer (Downs et al., 1987; Divine, 1990; Divine et al., 1993; Divine and Hartman, 1996; Ward et al., 1995, 1996c), while excess leukemias occur in workers exposed to polymer (Matanoski et al., 1990, 1993; Santos-Burgoa et al., 1992; Delzell et al., 1996; Macaluso et al., 1996). Furthermore, the lymphosarcomas were observed in the monomer workers, who were probably exposed to higher levels of 1,3-butadiene for shorter periods of time (wartime workers) and not in long-term workers with low levels of exposures. A confirmation of this observation comes from the stop-exposure studies conducted by Melnick et al. (1990a). They observed that at a similar total exposure, the incidence of lymphoma was greater among mice exposed to higher concentrations of butadiene for a shorter period of time (625 ppm for 26 weeks) than among mice exposed to a lower concentration for a longer period of time (312 ppm for 52 weeks). Consequently, this suggests that it is the concentration of 1,3-butadiene rather than the duration of exposure that is important in the occurrence of lymphomas. There is a null relationship between exposure to 1,3-butadiene monomer and occurrence of leukemias that is observed in polymer workers. This may be due to very low exposures to 1,3-butadiene in monomer production workers or exposure to a necessary co/modifying factor or a confounding factor in SBR production workers. Data are currently lacking to confirm or refute any of these possibilities. The findings of Delzell et al. (1996) and Macaluso et al. (1996) are inconsistent with confounding by exposure to other chemicals. The findings of excess leukemias in SBR production workers are consistent with a causal association with exposure to 1,3 butadiene.

7.3.4. Criteria of Causal Inference

In most situations, epidemiologic data are used to delineate the causality of certain health effects. Several cancers have been causally associated with exposure to agents for which there is no direct biological evidence. Insufficient knowledge about the biological bases for diseases in humans makes it difficult to identify exposure to an agent as causal, particularly for malignant diseases when the exposure was in the distant past. Consequently, epidemiologists and biologists have provided a set of criteria that define a causal relationship between exposure and health outcome. A causal interpretation is enhanced for studies that meet these criteria. None of these criteria actually proves causality; actual proof is rarely attainable when dealing with environmental carcinogens. None of these criteria should be considered either necessary (except temporality of exposure) or sufficient in itself. The absence of any one or even several of these criteria does not prevent a causal interpretation. However, if more criteria apply, it provides credible evidence for causality.

Thus, applying the criteria of causal inference to the monomer and polymer cohort mortality studies and one nested case-control study in which risk of lymphohematopoietic cancers were assessed resulted in the following:

- Temporality . There is temporality of exposure to 1,3-butadiene prior to the occurrence of lymphosarcoma in monomer workers and leukemias in SBR workers.

- Strength of association . Strength of association between exposure and the occurrence of lymphosarcoma in the prewar period ranged from 154% to 477% higher risk among workers exposed to monomer as compared with the nonexposed general population (Divine, 1990; Divine et al., 1993; Divine and Hartman, 1996; Ward et al., 1995, 1996c). The excess risk of leukemia ranged from 43% to 127% higher among workers exposed to SBR in ever-hourly workers as compared with the general population (Delzell et al., 1996). Internal comparison of SBR worker population resulted in a 4.5-fold increased leukemia risk among the highest exposure group in the same cohort (Macaluso et al., 1996). The nested case-control study from the SBR cohort showed a 7.6-fold increase in the risk of leukemia (Matanoski et al., 1989, 1993; Santos-Burgoa et al., 1992).

- Consistency . Two cohort studies in monomer workers showed an increased risk of lymphosarcoma (Divine, 1990; Divine et al., 1993; Divine and Hartman, 1996; Ward et al., 1995, 1996c), while one cohort study (Delzell et al., 1996; Macaluso et al., 1996) (with a cohort derived from seven U.S. plants and one Canadian plant) and one nested case-control study (Matanoski et al., 1989, 1993; Santos-Burgoa et al., 1995) showed an excess risk of leukemia in SBR workers. The SBR workers cohort defined by Delzell et al. (1996) showed a fairly consistent association between exposure to butadiene and occurrence of leukemia across plants. Excesses for both lymphosarcoma as well as leukemia were observed by McMichael et al. (1974, 1976) and Meinhardt et al. (1982).

- Specificity . All monomer studies showed an increased risk of lymphosarcoma while SBR studies showed an increased risk of leukemia. Overall, they show increased risks of lymphohematopoietic system cancer among populations exposed to 1,3-butadiene. It should be noted that exposure to a particular chemical (or drug or radiation) may cause more than one type of leukemia or another type of hematopoietic cancer (Linet, 1985).

- Biological gradient . The biological gradient, which refers to the dose-response relationship, was observed only in SBR workers. Both the nested case-control study and the cohort study showed increasing risk of leukemia with increasing exposures. Such a relationship was not observed in monomer workers. The reason may be because a very small number of people were exposed to high levels of 1,3-butadiene for a shorter period of time who showed the occurrence of lymphosarcoma. They could not be further stratified to evaluate the dose response.

- Biological plausibility . As described in Chapter 4, hemoglobin adducts have been detected in humans exposed to 1,3-butadiene (Osterman-Golkar et al., 1993; Sorsa et al., 1996). Significantly increased frequencies of hprt mutant lymphocytes were observed in high-exposure groups by Legator et al. (1993) and Ward et al. (1994). Mutations, chromosomal aberrations, and cell transformations, all well-established steps in the process of carcinogenesis, were observed in human and animal studies. This makes a convincing argument for the biological plausibility of occurrence of leukemia in SBR workers and lymphosarcoma in monomer workers.

In conclusion, some of the causality criteria apply to monomer workers and occurrence of lymphosarcoma while all the criteria apply well for leukemia among SBR workers. Based on strength of association, dose-response relationship, specificity of cancer (leukemiaCspecific cell type is not known at this time), and biological plausibility, there is sufficient evidence to consider 1,3-butadiene a known human carcinogen.